Evaluation of activated protein C resistance in women undergoing in-vitro fertilization treatment

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INTRODUCTION

- Ovarian stimulation prior in-vitro fertilization (IVF) causes a significant increase in serum estradiol levels which may influence hemostasis.
- Activated protein C (APC) resistance is a sensitive coagulation biomarker to the use of hormonal therapies (e.g., combined oral contraceptives (COC))

AIM

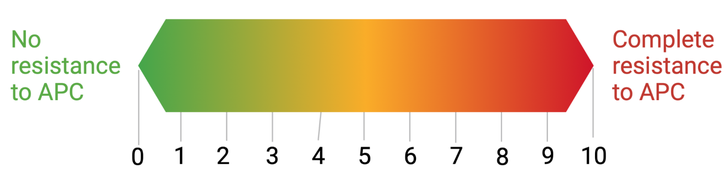
To assess the resistance towards the APC in women undergoing ovarian stimulation for IVF, using the endogenous thrombin potential (ETP)-based APC resistance assay .

METHOD

- Resistance to APC was assessed on the Calibrated Automated Thrombogram (CAT) with Thrombinoscope software (version 5.0), using commercially available CE-marked thrombin generation dedicated kit reagents from Diagnostica Stago.
- Ten women undergoing ovarian stimulation for IVF were enrolled and displayed the following characteristics (**Table 1**):

- The investigated thrombin generation parameter was the endogenous thrombin potential (ETP), corresponding to the area under the thrombin generation curve.
- Resistance to APC was expressed in normalized APC sensitivity ratio (nAPCsr) computed as following:

$$\frac{Sample\ ETP\ (+APC) \,/\, Sample\ ETP\ (-APC)}{Reference\ plasma\ ETP\ (+APC) \,/\, Reference\ plasma\ ETP\ (-APC)}$$



Patient	Age	BMI	Genetic mutation ?	Hormonal treatment	Composition	Treatment duration
01	33	24,7	n/d	Menopur 150	Menotropin (HMG)	12 days
02	38	16,1	NO	Meriofert 150	Menotropin (HMG) + hCG	20 days
03	29	15	FVL hetero	Puregon 100	Follitropin beta (recombinant FSH)	10 days
04	34	16,9	NO	Menopur 150	Menotropin (HMG)	12 days
05	31	20,5	NO	Gonal F 300 Progynova	Follitropin alpha (recombinant FSH) Estradiol valerate 2 mg	10 days
06	38	20	NO	Progeffik 100 Prontogest 100	Progesterone Progesterone	10 days
07	36	16,3	G20210A hetero	Gonal F 300 Ovitrelle	Follitropin alpha (recombinant FSH) Choriogonadotropine alfa (hCG)	12 days
08	31	17,1	NO	Progeffik	Progesterone	10 days
09	36	19,4	G20210A hetero	Gonal F 300 Menopur 75	Follitropin alpha (recombinant FSH) Menotropin (HMG)	15 days
10	37	16,3	NO	Progeffik 200	Progesterone	10 days

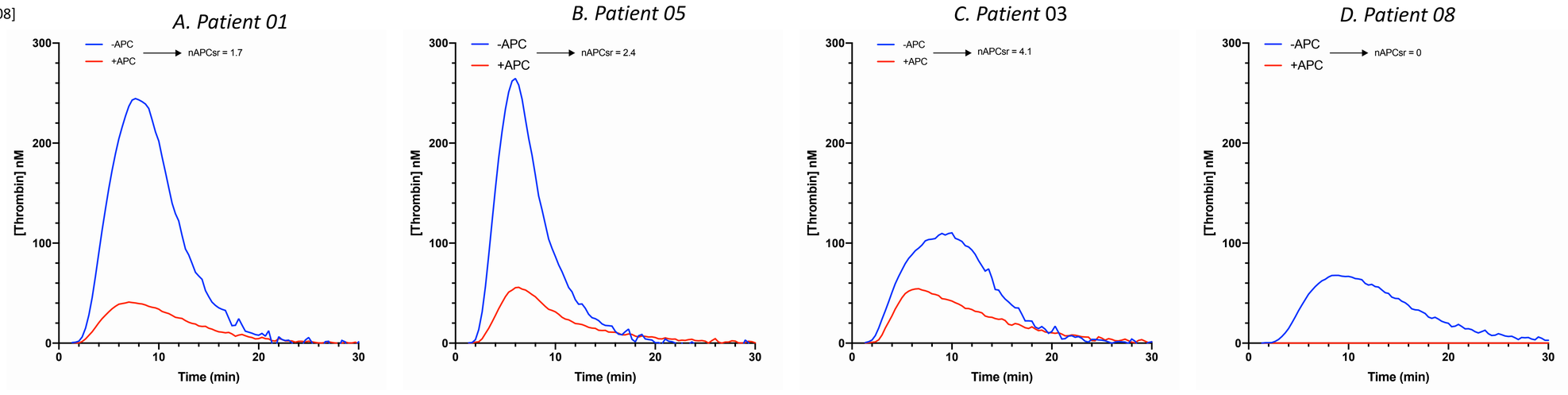
Table 1: Characteristics (age, BMI, genetic mutation, hormonal treatment, its composition and duration of treatment) of patients included.

RESULTS

Table 2: nAPCsr values of patient samples. Normal ranges stand between [0-2.08]

Patient	nAPCsr	Normal?
01	1.7	Yes
02	1.3	Yes
03	4.1	No
04	1.8	Yes
05	2.4	No
06	0.0	Yes
07	1.5	Yes
08	0.0	Yes
09	0.0	Yes
10	1.7	Yes

Figure 1 : Thrombin generation in absence of APC (blue curve) and in presence of APC (red curve) for patients 01, 05, 03 and 08.



DISCUSSION

- Ovarian stimulation appeared to have little impact on APC resistance. The majority of results were within the normal ranges of 0 to 2.08 (**Figure 1A and Table 2**)
- A resistance to APC was expected for patient 03 as she is carrier of a heterozygous factor V Leiden mutation (**Figure 1C**).
- The slight resistance to APC observed for patient 05 could be related to the use of estradiol (Progynova)(**Figure 1B**)
- The patient 08 had an abnormally low thrombin generation curve without APC. This could be explained by the use of an anticoagulant drug (**Figure 1D**)

CONCLUSION

This pilot study showed that ovarian stimulation with FSH agonist (HMG or follitropin) had little impact on APC resistance. On the the other hand, estradiol seemed to induce a slight APC resistance, which has already been observed in women using estradiol-containing COC. However, further investigations are needed to confirm these results.

PERSPECTIVES

- An anti-Xa activity test will be performed for patient 08.
- Dosage of FII, FVIII, protein S and protein C will be performed for all samples

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